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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,008	11/17/2003	Masaaki Ikeda	64517.000002	5744

21967 7590 11/18/2005

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EXAMINER	
GARVEY, TARA L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,008	IKEDA ET AL.	
	Examiner	Art Unit	
	Tara L. Garvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *7-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/1/03, 3/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending.

Election/Restrictions

Claims 7-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 21, 2005.

Applicant's election with traverse of Group I (claims 1-6, 16 and 17) in the reply filed on October 21, 2005 is acknowledged. The traversal is on the ground(s) that a search burden does not exist because the groups contain overlapping subject matter and in particular the vectors of Group II are used in the method of Group I. This is not found persuasive because while searches may partially overlap, they also extend beyond one another. In, for example, the case of a product and a process of using that product, a reference may exist that teaches the product of Group II drawn to recombinant vectors comprising a cyclin or a cyclin dependent kinase, but does not teach the same method of using this product as claimed in Group I, which is drawn to a method of proliferating a terminally differentiated cell. In the case of Group I and Group III, Group III comprises a product drawn to a mammalian cell or tissue, which can be obtained by a method other than Group I. In the case of Group I and Group IV, the method of Group I is not generic to the method of Group IV because art that anticipates Group IV may not anticipate Group I since Group IV only requires that a cyclin be

introduced, while Group I requires that both a cyclin and cyclin dependent kinase be introduced. Furthermore, the method of Group I is not limited to treatment of cardiopathy in a patient as is claimed in the method of Group IV. Claim 14 is in Group IV.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claim 2 is objected to because of the following informalities: In line 3, the word "lease" should be "least". Appropriate correction is required.

Claim 4 is objected to because of the following informalities: In line 2, add "a" before "mammalian". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of proliferating cardiomyocytes *in vitro* by introducing adenoviral vectors expressing a D-type cyclin, CDK4 or CDK 6 and a nuclear localization signal, does not reasonably provide enablement for an *in vitro or in vivo* method of proliferating any terminal differentiated cell by introducing any cyclin and any cyclin dependent kinase into the cell. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, relative skill in the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claim, with the most relevant discussed below.

Nature of the invention: The claims are directed to a method of proliferating terminal differentiated cells either *in vitro or in vivo* by delivering a cyclin and a cyclin dependent kinase (CDK) to the nucleus of the cells.

Breadth of the claim: The claims are very broad in that they are drawn to proliferating any terminally differentiated cell either *in vivo or in vitro* by introducing any cyclin and any cyclin dependent kinase into the nucleus of the cells.

Guidance in the specification/Existence of a working example: The specification provides a working example for proliferating cardiomyocytes by introducing adenoviral vectors expressing cyclin D1 attached to a nuclear localization signal and CDK4 into the nucleus of rat cardiomyocytes *in vitro* and into the apical region of a rat heart *in vivo*. The specification does not provide any guidance on the proper cyclin and CDK combination to use to obtain proliferation of all other terminally differentiated cell types. In addition, the specification has not provided evidence of introducing the cyclin and

CDK genes into quiescent cells by methods other than recombinant adenovirus transduction or obtaining proliferation of the terminally differentiated cells without a nuclear localization signal attached to the cyclin. Furthermore, the *in vivo* model for proliferation of terminally differentiated cells is not cell type specific since the injection of the cyclin D1/NLS and CDK4 adenoviral vectors into the rat heart resulted in expression of the Ki-67 nuclear protein (i.e. protein marker of proliferation) in both cardiomyocytes and non-cardiomyocytes and therefore, the specification has not demonstrated targeted expression of the genes *in vivo* to cause the proliferation of only a particular cell type. In terms of the *in vivo* proliferation of terminally differentiated cells, the specification has not taught the amount of expression necessary to produce proliferation, the dose of cyclin and CDKs to be delivered to the cells or how to target the expression of the proteins to only the desired cells. The lack of guidance would require trial and error experimentation to determine these factors.

State of the art/Predictability of the art: The art at the time of filing has recognized that specific cyclins interact with specific cyclin dependent kinases (CDKs) at specific times in the cell cycle. The specific cyclin and CDK pairings do not all have a proliferative effect in all cell types and are often essential only in specific cell types. For instance, the D-type cyclins activate CDK4 or CDK6, while the E-type cyclins activate CDK2 (Pagano et al. Cell (2004) volume 118, pages 535-538, see abstract, page 535, left column, paragraph 1 and right column, paragraphs 2-3 bridging page 536, page 536, Table 1, page 537, left column, first full paragraph). Therefore, any combination of

cyclin and CDK will not necessarily result in proliferation of any terminally differentiated cells.

In terms of inducing proliferation of terminally differentiated cells *in vivo*, several problems exist. First, promoting overexpression of cyclins and CDKs in cells, especially *in vivo*, may result in deregulation of the cell cycle, which can lead to tumorigenesis or to hyperproliferation of cells. For example, overexpression of cyclin D1 in particular is known to be responsible for breast cancer and abnormal CDK expression has been described for proliferation of vascular smooth muscle cells leading to restenosis (Brooks et al. Drug Discovery Today (1999) volume 4, number 10, pages 455-464, see especially 456, Figure 1, page 457, right column, paragraphs 3-4, page 458, Table 1, left column, paragraph 2 and right column, paragraphs 1-2 bridging page 459, page 459, Figure 2, page 460, left column, paragraph 2).

Second, the method of *in vivo* induction of proliferation of terminally differentiated cells involves gene therapy with the potential to repair damaged tissue. At the time of filing, the prior art demonstrates that treating a disease by a method of gene therapy was not routine. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and targeted expression of the protein at predictable and effective levels, created technical barriers to the practice of gene therapy methods. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery" (Verma et al. (1997)

Nature Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY) explains, "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82).

The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy,1996, Volume 7, pages 1781-1790, see page 1789, column 1, first paragraph). Thus, the art clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see "3. Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. Thus, as of the filing date of the instant application, gene therapy was regarded as unsuccessful and unpredictable.

Quantity of experimentation: A large amount of experimentation would be necessary to determine the cyclin and the CDK that would be able to promote

proliferation of every terminally differentiated cell type either *in vitro or in vivo*. Furthemore, the art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease. The skilled artisan would not be able to use the methods in the instant claims to proliferate terminally differentiated cells *in vivo* without a large amount of trial and error experimentation to determine ways to achieve targeted expression at levels necessary to proliferate a sufficient amount of the correct cells for a therapeutic effect.

Conclusion: In order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed protein, to select a proper dose or to determine other factors to successfully proliferate terminally differentiated cells *in vivo*. The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy methods. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-2917. The examiner can normally be reached on Monday through Friday 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Tara L Garvey
Examiner
Art Unit 1636

TLG

DANIEL M. SULLIVAN
PATENT EXAMINER